REMARKS/ARGUMENTS

Claims 134, 139-143, 145 and 148-175 are active in this application.

Support for the Amendments

Claim 134 has been amended to incorporated Claim 136.

The term "region" has been replaced with "end" in claims 139, 140, 142, 157 to 162. Support for these amendments can be found at least page 9, lines 1 to 10 where in referencing figure 4 the "C-terminal region"-region IV means " C-terminal end.

The phrase "a merozoite form of MSP-1 protein" has been changed to "MSP-1 protein of a Plasmodium parasite" in claims 139, 143 157 to 159 which finds support on page 9, lines 1 to 15.

Support for the amendment to Claims 151, 152 and 153 is found in the Sequence Listing on file in this application as well as on page 16, referring to Figure 1A (Claim 151); on page 17 referring to Figure 1B (Claim 152). The remaining claim amendments are provided to improve readability and for clarity.

The specification has been amended to include Sequence Identifiers ("SEQ ID NO:") where appropriate, support for which is found in the Sequence Listing of record in this application (addressing the item noted on page 2 of the Official Action). The specification has also been amended to include additional description of the drawings which is supported on pages 37-38 of the application as originally filed (addressing the item noted on pages 2-3 of the Official Action).

No new matter is added.

The rejection in view of Holder (U.S. 5,720,959)

While Holder describe the cloning of specific polypeptide sequence of MSP1, Holder does not describe a 19 kilodalton (p19) C-terminal fragment of the MSP-1 protein, which has the atomic coordinates in Annexes I or III; and the NMR fingerprints of Figures 12.0a to 12.0c or 12.2a to 12.2 (see Claim 134 as amended herein).

It is well-established law that in order for a reference to anticipate a claimed invention, the reference or references must provide an enabling disclosure sufficient to place the public in possession of the claimed invention.[1] However, Holder does not describe nor provides any guidance as to how to obtain a recombinant protein of such a purity that would permit one to establish the atomic coordinates and/or NMR fingerprints as defined in Claim 134. As discussed in the present specification to obtain an NMR "fingerprint" of a protein, the protein must be pure to at least about 95 %, since the signals of any proton-containing contaminant present at substantial concentrations would be observed in 1H NMR spectra (page 42, lines 24 to 27). As Holder fails to enable obtaining such a purity, the claimed invention cannot be anticipated by thereby.

Therefore, withdrawal of the rejection of Claims 134 to 137, 139 to 143, 148 and 150 under 35 U.S.C. 102(e) in view of Holder et al., is requested.

The rejection in view of Longacre (1995) and Longacre (1994) +/- Holder

The combination of Longacre 1995 and 1994 fail to describe or suggest the recombinant protein having a 32 amino acid leader sequence (see Claim 153(a)) and a MSP1 C-terminal fragment containng amino acids 276 (K) to 380 (S) of SEQ ID NO:11. This point is further elaborated below.

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[1]See MPEP 2121.01 and *In re Hoeksema*, 399 F.2d 269, 158 USPQ 596 (CCPA 1968).

Longacre (1995) describes the homology of *Plasmodium cynomolgi* MSP-1 protein C-terminal sequence with other *Plasmodium* species. In Figure 1 the homologies between the 42- kilodalton and 19- kilodalton fragment is illustrated. The cloned vectors described in Longacre (1995) have the same signal sequence as those described in Longacre et al. (1994), see Figure 1.

The C-terminal region of MSP-1 that was sequenced includes Regions I, II, III and IV and encompasses 380 amino acids. There is no suggestion in Longacre et al. to use a shorter MSP-1 C-terminal sequence and certainly not one in which the *Plasmodium cynomolgi* sequence is from Lys $_{276}$ to Ser $_{380}$ of SEQ ID NO:11 as defined in Claim 153. In fact, Longacre (1995) would not have been modified to select a shorter sequence because the publication suggests that the entire sequence of amino acids 1 to 380 may be used as a vaccine; not a sequence of *P. cynomolgi* as claimed. (see MPEP 2141.02 : "A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention").

Combining Longacre et al. (1994) with the 1995 publication does not provide any further suggestions for the claimed recombinant protein. Specifically, Longacre et al (1994) describes producing *Plasmodium vivax* merozoite surface protein 1 C-terminal recombinant proteins in baculovirus of 42 kDA or 19 kDA C-terminal fragments of MSP-1. This description does not correspond to the 19kD C-terminal fragment as claimed (see Claim 153) and provides no suggestion to modify the sequence in the 1995 publication.

Furthermore, the constructs described in the 1994 publication contained a 8 bp leader sequence and a 33 amino acid which included a signal sequence from *P. vivax*. However, the recombinant protein claimed in Claim 153 requires a 32 amino acid leader sequence from *P. vivax*.

There is nothing in the 1994 and 1995 publications, when combined, which provide any suggestion or motivation to modify both the leader sequence and the C-terminal fragment of MSP1 to be the same as that defined in Claim 153(a) and (b).

Therefore in view of the above, withdrawal of the rejection of Claims 153, 156, 159, 165, 169, 172 and 175 under 35 U.S.C. § 103(a) based on Longacre (1995) and Longacre (1994) is requested.

Concerning the combination of Longacre 1995 and 1994 with Holder, this combination of publications also fails to describe or suggest the invention claimed. Specifically, The references themselves do not describe modifying the specific disclosures of each or any suggestion that for the advantages of the claimed composition. Furthermore, the proteins of Longacre (1994 and 1995) would not have been modified by Holder because each specifically relates to the discovery of an optimized composition, i.e., specific polypeptide, polypeptides and combination thereof, to achieve a desired goal.

There is nothing in either cited publication which suggests or provides the requisite motivation for modifying the described polypeptide or fragments absent the description provided in the present application. The Examiner has not offered any evidence as to why such a combination would have been obvious. Rather, each of the disclosures is limited to their unique findings and provides no indication or suggestion whatsoever that the disclosures would be applicable in other combinations and configurations as the one claimed in this application.

Withdrawal of the rejection of Claims 134-37, 139-141, 143, 145, 148, 149 and 150 under 35 U.S.C. § 103(a) based on Longacre (1995), Longacre (1994) and Holder is requested.

The rejection in view of Chappel, Miller, Longacre (1994) and Longacre (1995) +/- Holder

These combinations of cited publications do not describe or suggest a recombinant protein having a 32 amino acid leader sequence of MSP-1 from *P. vivax* (see Claims 151 (a) and 152 (a)) and a C-terminal fragment of MSP-1 from position 3 to position 95 of SEQ ID NO:1 (see Claim 151(b)) or from position 3 to position 116 of SEQ ID NO:4 (see Claim 152(b)).

Chapppel describes a recombinant construct having the N- terminal 34 amino acids of the *P. falciparum* MSP-1 protein fused to 271 amino acid residues of the p42 fragment of this protein ending at residue 1723 (as numbered in Miller). Chapppel does not describe the fragment of 92 amino acid sequences from *P. falciparum* as claimed in Claim 151 or 113 amino acids as in Claim 152. Chappel do not suggest to the skilled artisan to alter or modify any of their constructs, since monoclonal antibodies that inhibit *Plasmodium falciparum* invasion *in vitro* recognized 2 regions in these constructs which are related to epidermal growth factor. Thus, the constructs described in Chappel et al "may have a potential for development into a vaccine against blood-stage malaria."

Longacre (1994 and 1995) describe specific constructs, as discussed above, and do not suggest that any C-terminal fragments of the MSP-1 protein of any length can be expressed using an MSP-1 signal sequence. Indeed, at page 194, second column Longacre emphasized that the constructs were designed such that the probable sites for *P. vivax* MSP1 terminal processing was obtained, both in the 42- kDa construct and the 19 kDa construct. More specifically, Longacre (1994) states at page 194 the following:

> Having determined probable sites for *P. vivax* MSP1 terminal processing, we designed the constructs to **code for an additional six or seven residues upstream from these sites. Judging from the relative conservation of these residues among the four species, we supposed that they might contain important elements for the processing even itself which could be used to generate protective antibodies that might inhibit processing** (emphasis added).

From this, one would acknowledge that constructs of less than 96 or 95 amino acids would probably not generate protective antibodies. Hence Longacre would teach away from using a shorter construct as described in the presently claimed invention.

There is nothing in the combination of publications cited which suggests or provides the requisite motivation for modifying the described polypeptide or fragments absent the description provided in the present application. Rather, each of the disclosures is limited to their unique findings and provides no indication or suggestion whatsoever that the disclosures would be applicable in other combinations and configurations as the one claimed in this application. Moreover, even if a modification was in fact made there is no teaching or suggestion in these publications as to how one should modify the recombinant constructs or whether these modified constructs would in fact have successfully inhibited parasitemia ***in vivo***. Indeed, as noted above, the Longacre (1994) publication teaches not to modify the C-terminal construct from P19 to less than 96 or 95 amino acids because of terminal processing sites.

Furthermore, Chappel and Miller , as with the Longacre references, do not describe nor provides any guidance as to how to obtain a recombinant protein of such a purity that would permit one to establish the atomic coordinates and/or NMR fingerprints as defined in Claim 134.

Therefore, the claimed invention would not have been obvious in view of the combination of cited publications. Withdrawal of the rejection of Claims 151, 154, 155, 157, 158, 160, 161, 163, 164, 166, 167, 168, 170, 171, 173 and 174 under 35 U.S.C. § 103(a) in view of Chappel, Miller, Longacre (1994) and Longacre (1995) is requested.

Holder, when combined with the above noted publications, does not provide any further basis on which to allege that the claimed invention would have been obvious.

Specifically, as discussed above, Holder provides a description of specific recombinant molecules but does not provide any suggestion to modify the combined, specific teachings in Chappel, Miller, Longacre (1994), and Longacre (1995). Therefore, the rejection of Claims 134-37, 139-141, 143, 145, 148, 149 and 150 under 35 U.S.C. § 103(a) based on Chappel, Miller and Longacre (1995), Longacre (1994) and Holder should also be withdrawn.

The Rejection under 35 U.S.C. § 112, first paragraph

Claim 134 is defined by atomic coordinates and NMR fingerprints. Therefore, Claim 134 and the claims dependent therefrom are unquestionably described in the specification.

Claims 151, 152, and 153 are defined in (b) by a region of SEQ ID NO:1 (Claim 151); SEQ ID NO:4 (Claim 152); or SEQ ID NO:11 (Claim 153). Therefore, Claims 151-153 and the claims dependent therefrom are also unquestionably described in the specification.

With respect to Claim 145 and claims that depend from Claim 145, this vaccinating composition is also described based on the description provided in the specification and the knowledge already available in the relevant field (noting that a patent application need not contain those items which were known to those skilled in the art at the filing date of the present invention. *Vas-Cath, Inc. v. Mahukar,* 935 F.2d at 1563, 19 USPQ2D at 116 (Fed. Cir. 1991)). Thus, the question with respect to Claim 145 is whether one would recognize that the Applicants were in possession of the invention claimed therein.

It was known prior the filing of the present invention that only 4 types of *Plasmodium* species can cause malaria, which are *Plasmodium falciparum*, *Plasmodium vivax*, to a lesser extent, *Plasmodium malariae* and to even a lesser extend *Plasmodium ovale*.

The C-terminal fragment was known to be highly conserved in various *Plasmodium* species as described by Longacre (1995) and also depicted in the alignment presented in

Figure 4 of the present application. The epitope domains of the C-terminal 19 kilodalton fragment are described in the present application, for example, on page 9, lines 16 to 20. The examples of the present application clearly demonstrate the inhibition of parasitemia when using the described constructs (see at least pages 24 to 30 of the present application).

Therefore, based on the description of the epitope domains described in the application their correlation with the function of inhibiting parasitemia and the conserved amino acid sequences of the pathogenic *Plasmodium* species, there can be no question that one would recognize that the Applicants were in possession of the invention claimed in Claim 145.

Withdrawal of the rejection of Claims 134-137, 139-143, 145, 148-175 under 35 U.S.C. § 112, first paragraph is requested.

The rejection under 35 U.S.C. § 112, second paragraph

In Claims 134 and 137 the terminology "human antisera" has been deleted; Claim 137 has been canceled; "region" has been deleted from claims 139 and 140. p33 has been further defined as being from the MSP-1 protein. In claims 143 and 150, antecedent basis is now found for the terms "membrane: and MSP-1 protein; and "essential constituent" has been deleted from the claims.

Claims 151 to 153 have been amended to include sequence identifiers (SEQ ID NO:).

In claims 153 and 154, the claims now recite (a) and (b); the term "region: has been deleted from claims 157 to 159; antecedent basis is now present for the terms "cleavage" and "MSP-1 protein" for claims 160-162 and 166. The typographical errors have been corrected in Claims 154 and 174.

With respect to the rejection of the term p33, the essential inquiry pertaining to the requirement under 35 U.S.C. § 112, second paragraph is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness of claim language must be analyzed, not in a vacuum, but in light of:

(A) The content of the particular application disclosure;

(B) The teachings of the prior art; and

The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. See MPEP § 2173.02.

p33 has been defined as being from the MSP-1 protein. Furthermore, it was well known in the art at the time of the filing of the present application that the p33 protein is the N-terminal fragment associated with p19 in the corresponding p42 before natural cleavage of p42 into the MSP-1 protein. Figure 4 in the present application illustrates p33 as corresponding to the region III, while region IV in this Figure is the p19 of MSP-1. Thus, one of skill in the art can clearly be understood.

In view of the above, withdrawal of this rejection is respectfully requested.

Applicants request that the present application be passed to issuance without further delay.

Respectfully submitted,

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